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Research Paper

Challenge of paediatric compounding to solid dosage forms sachets and hard capsules – Finnish perspective

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Abstract

Objectives: The study evaluated the quality of compounded sachets and hard gelatine capsules and their feasibility in paediatric drug administration.

Methods: Commercial tablets were compounded to sachets and capsules in hospital environment, and the uniformity of content and simulated drug dose were determined.

Key findings: Compounded formulations were successfully obtained for a range of drug substances; dipyridamole, spironolactone, warfarin and sotalol formulations were within acceptable limits for uniformity of content, in most cases. Though, some loss of drug was seen. The type and amount of excipients were found to affect uniformity of content; good conformity of capsules was obtained using lactose monohydrate as filler, whereas microcrystalline cellulose was a better choice in sachets. In capsules, content uniformity was obtained for a range of drug doses. If the drug is aimed to be administered through a nasogastric tube, solubility of the drug and excipients should be considered, as they were found to affect the simulated drug dose in administration.

Conclusions: Compounded sachets and capsules fulfilled the quality requirements in most cases. In compounding, the choice of excipients should be considered as they can affect conformity of the dosage form or its' usability in practice. Quality assurance of compounded formulations should be taken into consideration in hospital pharmacies.

Keywords:

Capsule, Compounding, Content uniformity, Nasogastric tube, Paediatric, Sachet

Introduction

The lack of age-appropriate formulations for paediatric medications is faced in everyday work in hospitals. Also, off-label use of medicines is common (1,2). In medication, *extemporaneous* preparations have to be used, although these have certain risks such as dosing inaccuracy or errors, excipient toxicity or modified bioavailability (3). Dosage forms and formulations are needed for paediatric use. In dosage forms, critical issues are dosing flexibility, accuracy and their practical handling. It has been evaluated that these issues concern even a quarter of existing dosage forms (3). Improvement needs concern even half of the marketed drug products when the ease of intake and palatability of the dosage form are taken into account. In improving the pharmaceutical quality of paediatric medicines the priority is on the youngest age groups, neonates and infants. Fortunately, an increased trend in the marketing authorisation procedures has been seen recently (4).

Thus far, the need for compounding commercial products to paediatric dosage forms prevail in hospitals. The choice of dosage form type vary in different European countries (5). Liquid preparations are predominant in England and Sweden, capsules in France and powders in Finland. Also other manipulations, such as tablet splitting into segments or opening capsules are often necessary in paediatric medications (6), but risk for dose inaccuracy and chanced bioavailability is apparent in these manipulations (7,8,9). Facilities, time and expertise in hospital pharmacies limit the choice of what kind of compounded dosage forms are usually prepared (5). The practice in manufacture varies in the hospitals throughout Europe and there is little harmonisation of formulations. Many formulations are developed in-house, based on the literature available (if any). The quality of the formulations is usually evaluated indirectly, based on the batch records of procedures and ingredients. Often limited facilities are available for quality assurance, such as analytical equipment for evaluations of uniformity of content or stability of the drug.

In Finland, compounding to solid dosage forms is common in hospital pharmacies; a commercial tablet is crushed and diluted with an appropriate filler and redistributed in smaller

strength sachets (powder paper) or capsules to obtain appropriately sized dosage units for paediatric medication (10). In practice, compounding to solid dosage forms has been considered feasible because solids are suitable for drug substances that are unstable in aqueous environment and thus cannot be compounded to suspensions or solutions (11). In general, solid dosage forms are expected to have better stability of the drug, although only few results of stability studies have been published for compounded capsules (12,13). Additionally, solid dosage forms may be preferable because less excipients are needed (14). This is important because many common excipients exhibit potential risk for toxicity in paediatric patients (15).

However, little published information exists on compounded oral solid dosage forms, sachets and capsules. The information is in-house knowledge, and may be limited due to the lack of analytical facilities in hospital pharmacies. A Finnish research group has studied compounded sachets and hard gelatine capsules of one drug, nifedipine (10,16,17). They concluded that the optimum powder mass in sachets should be 300 mg or more, in smaller powders drug loss during manufacture increase the risk for non-conformity and low drug recovery. On the other hand, it was possible to prepare small capsules (size numbers 3 and 4), which complied the standards for uniformity of content. A French study evaluated the effect of the amount of the active ingredient on conformity of capsules, concluding that small amounts of drug increase the risk for non-conformity (18). *Extemporaneous* formulations that meet the quality standards could be compounded in these studies, but not all the formulations were such. It is evident that more information is needed, on more drug substances as well as on formulations containing different kinds of excipients. Although compounded formulations should be avoided, they still need to be used in hospitals. Thus, all the work towards compounded products which would be safe in use is extremely important.

In the present study, the real life compounding of solid dosage forms in hospital pharmacy was mimicked, using the procedures and facilities available. The quality of sachets and hard gelatine capsules was evaluated, by determining their content uniformity as described in the European

Pharmacopoeia. Furthermore, the usability of the compounded solid dosage forms in paediatric drug administration was evaluated by mimicking the real administration procedure in hospitals (drug administration via nasogastric tube). In practice, the dosage form is opened before administration and the contents are administered with fluid or food (5). In the younger patients, the contents are suspended in water and administered through a nasogastric tube. Administration has been found challenging due to occasional blockage of the tube (19,20). The present study evaluated whether the formulation could explain difficulties in administration.

Commercial tablets were compounded to sachets and capsules with different drugs and excipients in formulations. Drug substances were chosen based on their prevalence as commonly modified products in Finnish hospital pharmacies; dipyridamole, spironolactone, warfarin and sotalol. Additionally, warfarin and spironolactone were chosen based on their status as drugs included on the WHO Model List of Essential Medicines for Children (21). Although these drug substances are widely used in paediatric medication, no published information on the quality of compounded sachets or capsules is available. The risk for non-conformity was expected to be most evident with small-dose drugs (18). Thus, the effect of drug amount was studied with spironolactone and warfarin, which have the lowest therapeutic dose (of the four drugs). Sachets and capsules of different sizes were prepared, by varying the amount of filler in the formulation. Microcrystalline cellulose and lactose monohydrate were chosen because they are both widely used as excipients in paediatric medicines. Different grades of excipients were evaluated; microcrystalline cellulose, silicified microcrystalline cellulose and two grades of lactose monohydrate. These were chosen on the basis of their particle size and flow properties, which are expected to be important variables in preparation of the sachets and in the filling procedure of capsules which is standardized by volume (10). The effect of excipient grade was evaluated in more detail with sachets of the smallest weight. As the sachets are filled with weight, small weight sachets are expected to be most sensitive to dose non-conformity.

Materials and methods

Materials in compounding

Commercial tablets were compounded to sachets and hard gelatine capsules. Drug substances in these were dipyridamole (Dipyrin 75 mg, Ratiopharm; Merckle, Germany), spironolactone (Spirix 25 mg, Takeda Pharma, Denmark), warfarin as a sodium salt (Marevan forte 5 mg, Orion Pharma, Finland) and sotalol as a hydrochloride salt (Sotalol Mylan 80 mg, Mylan; Gerard Laboratories, Ireland).

Microcrystalline cellulose (MCC; Avicel PH-102, FMC Biopolymer, Ireland), silicified microcrystalline cellulose (SMCC; Prosolv 50, Penwest Pharmaceuticals Co, USA) and two grades of lactose monohydrate (Pharmatose, 200M and 80 M, DMV International, Netherlands) were used as fillers in formulations. Lactose monohydrate is freely but slowly soluble in water (1 in 5.24) whereas the celluloses are practically insoluble in water (22). In the MCC the average particle size was 100 µm and the values for bulk density and tapped density were 0.32 g/cm^3 and 0.48 g/cm^3, respectively. In the SMCC the corresponding values were 60 µm, 0.31 g/cm^3 and 0.39 g/cm^3. In Pharmatose 200 M the particle size was < 250 µm (fine particle fraction 60% < 45 µm) and values for bulk and tapped densities were 0.55 g/cm^3 and 0.85 g/cm^3, respectively. In Pharmatose 80 M the particle size was < 355 µm (fine particle fraction 10% < 100 µm), and the respective values for bulk and tapped densities were 0.76 g/cm^3 and 0.91 g/cm^3.

Compounding to sachets and hard capsules

Preparation of the sachets and hard capsules were done according to the standard protocol for *extemporaneous* compounding of dosage forms in hospital pharmacy, using the equipment and facilities available (Helsinki University Hospital, Finland, Päijät-Häme Central Hospital, Finland). Manufacturing procedures are the same in these units, but the choice of excipients in formulations

differ slightly (lactose is preferred in the first unit whereas MCC in the second).

The commercial tablets were crushed manually and carefully ground into a fine powder, with a pestle in a non-porous mortar. The pestle was held firmly and downward pressure was exerted with it while the pestle was moved in concentric circles. Geometric amounts of filler were added to achieve a final drug concentration in formulation. Sachets were prepared to total weight of 200 mg (dipyridamole), 300 mg (sotalol) or 500 mg (spironolactone or warfarin). The theoretical amount of each drug was 5 mg (dipyridamole), 4 mg (sotalol), 0.5 mg (spironolactone) and 0.1 mg (warfarin). Each powder was weighed individually using an analytical balance (precision ± 0.05 mg) and transferred into waxed powder papers (Ulvila Paper Mill, Finland). One batch of each formulation was prepared for the production of 100 sachets.

In preparation of the capsules, the amount of filler needed to fill the capsule was calculated and geometric amounts of filler were added to ground tablet mass to achieve the final volume of capsules. Hard gelatine capsules number 0 (volume 0.68 ml) were used for spironolactone and warfarin formulations, and capsules number 1 (volume 0.5 ml) were used for sotalol formulation. The theoretical amount of the drug in capsules was the same as in the sachets. Additionally, capsules containing higher amounts of drug were prepared for spironolactone and warfarin. Drug doses were 4 mg for sotalol, 0.5 mg, 3 mg and 6 mg for spironolactone and 0.1 mg, 0.2 mg and 2 mg for warfarin. Capsules were filled with the Feton Fastlock capsule filling machine (Feton International, Belgium). Parallel batches were prepared for the production of 100 hard capsules. Because the capsules are filled with volume, variation in the powder mass and thus variation in the filling procedure may result in batch to batch variability.

As a comparison to the semi-automated procedure (Feton) which is commonly used in Finnish hospitals, capsules were prepared with an automated procedure. These capsules were manufactured by Mettler Toledo Gmbh (Switzerland), using an automated Quantos capsule filling device (QH012-LNM, Mettler Toledo AG, Switzerland). The powder mass was prepared in hospital

pharmacy, as described previously, and the obtained drug powder was sent to Mettler Toledo for capsulation. The reference capsules contained the lowest amount of drug; spironolactone (0.5 mg) or warfarin (0.1 mg).

Drug analysis by HPLC

Drug concentrations were determined by means of high performance liquid chromatography (HPLC). Previously described methods with slight modifications were used in analysis (dipyridamole (23), spironolactone (24); warfarin sodium (25); sotalol hydrochloride (26)). Samples containing sotalol hydrochloride were analysed in the Department of Environmental Sciences, all the other drugs were analysed in the Division of Pharmaceutical Chemistry and Technology.

The HPLC system (Shimadzu Corporation, Japan, for sotalol hydrochloride; Thermo Separation Products TSP, USA, for the other drugs) consisted of degasser (Shimadzu DGU-20 A5; TSP Spectra System SCM 1000 vacuum membrane degasser), a pump (Shimadzu LC-20AT; TSP Spectra System P4000), autosampler (Shimadzu SIL-20-A; TSP Spectra System SA 3000), a UV-VIS detector (Shimadzu SPD-20A; TSP Spectra System UV 6000 LP) and a computerized data analysis system (Shimadzu Corporation LabSolutions 5.57 SP1, Japan; CromQuest 4.2.32, Thermo Scientific, USA).

Sample separation was carried out in a reverse phase C-18 column (Synergi Hydro-RP 4.6 mm x 25 cm; 4µm, USA for sotalol hydrochloride; Supelco Discovery 4.66 mm x 15 cm; 5 µm, USA for the other drugs). Retention times varied from 4.3 to 4.7 minutes for the analytes.

The mobile phase consisted of methanol and phosphate buffer pH 4.6 (in a ratio of 75:25) for dipyridamole. For spironolactone, the mobile phase was methanol and HPLC grade water (65:35). For warfarin sodium, the mobile phase consisted of acetonitrile and HPLC grade water with 0.05% of trifluoroacetic acid (55:45). For sotalol hydrochloride, the mobile phase was acetonitrile and phosphate buffer pH 4.6 (75:25). The flow rate of the mobile phase was 1.0 ml/min.

197

198 *Uniformity of content*

199 Content uniformities of dosage units (commercial tablets and compounded solid formulations
200 thereof) were determined by method established in the European Pharmacopoeia. The dosage unit
201 complied the test if not more than one of 10 individual contents was beyond ±15% of the average
202 content and if none were beyond ±25% of the average content. If two or three individual contents
203 deviated more than ±15% (but less than ±25%), the individual contents of another 20 dosage units
204 were determined. The drug concentrations were analysed in triplicate by HPLC.

205

206 *Statistical analysis*

207 Statistical analysis were carried out in SPSS (IBM SPSS Statistics, Ver. 23, United States)
208 using non-parametric Kruskal-Wallis analysis of variance. Individual differences were identified
209 using Dunnet's two-tailed t-test as a post hoc test. The value $P<0.05$ was considered as statistically
210 significant.

211

212 *Simulation of drug administration*

213 Dosage form administration to paediatric patients in hospitals was simulated mimicking the
214 administration procedure through a nasogastric tube (Helsinki University Hospital, Finland, Päijät-
215 Häme Central Hospital, Finland). Individual contents of the dosage forms were emptied to a
216 medicine cup and suspended to HPLC grade water. The volume of water varied depending on the
217 procedure that they use in the hospital; 1.5 millilitres of water was used for suspending the contents
218 of size 1 hard gelatine capsules, and for suspending the contents of size 0 hard gelatine capsules or
219 sachets the volume was 3 millilitres. The suspension was thoroughly stirred with the tip of an oral
220 syringe (volume 5 ml) after which the formed suspension was withdrawn into the syringe for drug
221 administration. Nasogastric tube (Nutrisafe 2, size 06 French/50 cm, internal diameter 1.2 mm,

external diameter 2 mm, VYGON, France) was first rinsed with 2 millilitres of water, after which the drug suspension was administered through the tube. Finally, the tube was rinsed with 2 millilitres of water. All contents were led to a volumetric flask and after diluting the sample to a known volume, the amount of drug was analysed by HPLC. The simulated drug dose passed through the nasogastric tube was expressed as percentage of the average amount of the drug in formulation. The procedure was repeated in triplicate for each formulation.

Results

Content uniformity of commercial tablets

All commercial tablets complied the test for uniformity of content, as expected. The average contents of drug in tablets were 77.6 mg ± 3.5 mg (SD) for dipyridamole (103.5% of the theoretical drug amount, which was labelled to be 75 mg), 24.2 mg ± 0.3 mg for spironolactone (98% of the labelled amount 25 mg), 4.96 mg ± 0.08 mg for warfarin (99.2% of the labelled amount 5 mg) and 72.1 mg ± 1.4 mg for sotalol (90.1% of the labelled amount 80 mg).

Content uniformity of compounded sachets

The content uniformity of sachets, compounded with different fillers as excipients, complied the test for uniformity of content for most formulations (Table 1). However, if lactose of smaller particle size (< 250 µm) or microcrystalline cellulose were used as fillers, the formulation failed to comply with the test. In case of MCC formulations, two individual contents were outside the limits 85 per cent to 115 per cent of the average content, and one was outside the limit of 75 per cent to 125 per cent, in which case the deviation was 26.3% of the average content. For lactose formulation (particle-size grade < 250 µm), one content was outside the limit of 75 per cent to 125 per cent (measured value –30.7%). The average drug content in formulations containing the different

247 excipients (MCC, SMCC or lactose, two grades) was found statistically significantly different
248 ($P<0.05$) (Table 1).

249 Although most of the formulations complied the test for uniformity of content, the mean drug
250 content in compounded sachets was in most cases less than the theoretical drug content (Table 1).
251 The difference was statistically significant ($P<0.05$) for most of the formulations (5/7). The
252 adsorption of the drug in powder paper seemed one possible explanation for the loss of active
253 ingredient, as visualised in Figure 1 for the yellowish drug dipyridamole. At highest, 16% (0.8 mg;
254 SD ± 0.13 mg; n=5) of the labelled dose of dipyridamole was recovered from the sachet paper
255 (formulation containing lactose particle-size grade < 355 µm). In analysis, the paper was rinsed with
256 water and the drug analysed by HPLC. The drug loss was smallest when SMCC was used as filler in
257 sachets, 3.8% (0.2 mg; SD ± 0.02 mg; n=5) of the labelled dose of dipyridamole was recovered from
258 the sachet paper. The rest of the missing dose was assumed to be on the manufacturing tools.
259
260 *Content uniformity of compounded capsules*
261 The content uniformity of hard capsules compounded using lactose as filler complied the test
262 for uniformity of content (Table 2). Content uniformity of hard capsules of spironolactone and
263 warfarin were studied at three different dose levels. The largest single-capsule deviation from the
264 mean content was 21% for capsules that contained the lowest amount of spironolactone (0.5 mg). The
265 measured mean drug content in the batch was 0.42 mg which was lower ($P<0.05$) than the theoretical
266 amount of drug (84.4% of the labelled dose). Also for warfarin, the highest single-capsule deviation
267 (–8.2%) was observed with a batch of capsules which contained the lowest amount of drug (0.1 mg).
268 In the batch, the measured mean drug content was 90% of the theoretical amount of drug, although
269 the effect was not statistically significant in this batch.
270
271 If microcrystalline cellulose was used as a filler in hard capsules (drug sotalol), one batch out

of three did not comply the test for uniformity of content (Table 2). The highest single-capsule deviation was 25.2% which was slightly above the upper acceptation limit. In all batches the measured mean drug content was lower compared to the theoretical amount of the drug (4 mg). The average amount of drug varied from 3.7 mg (SD ± 0.09 mg, $P<0.05$) to 3.72 mg (SD ± 0.39 mg, $P<0.05$), which corresponded 92.5% to 93.0% of the theoretical amount of the drug.

In most cases, no statistically significant effects were found in relation to batch to batch variation. Only two batches out of 15 parallel batches differed significantly ($P<0.05$) in the average drug content (Table 2).

Capsules were also prepared with an automated Quantos capsule filling device, as a comparison to the conventional method (Feton). The batches prepared using Quantos complied with the content uniformity test specified in the European pharmacopoeia, as expected. Segregation of powder components during the filling process was not observed (Figure 2). The filling method had no effect on the quality of the capsules, and no statistically significant differences were found in the average drug content if capsules filled with Quantos were compared to capsules filled with the conventional method. The largest single-capsule deviation from the mean content was 10% (spironolactone 10.24%; warfarin 10.20%; filler lactose). The average amount of drug in capsules was 0.41 mg (SD ± 0.017 mg) for spironolactone and 0.093 mg (SD ± 0.0038 mg) for warfarin, which corresponded 82.0% and 93.0% of the theoretical amount of the drug (0.5 mg and 0.1 mg for spironolactone and warfarin, respectively). The difference in drug amount was statistically significant ($P<0.05$) for spironolactone (no statistical effects were found for warfarin).

Simulation of drug administration through a nasogastric tube

The loss of drug was evident when suspended formulations were lead through a nasogastric tube, mimicking the procedure used in hospitals in administering the drug to the paediatric patient. The lowest simulated drug doses were obtained with sachets that contained celluloses (MCC or

SMCC) as fillers, compared to formulations that contained lactose. In these, the amount of dipyridamole passed through the nasogastric tube (n=3) varied from 46.5% (SMCC) and 62.0% (MCC) to 77.5% (lactose < 355 µm) and 86.1% (lactose < 250 µm) of the average drug content.

In compounded hard gelatine capsules the drug loss was smaller than 12% of the average drug content in all cases. For size 0 hard gelatine capsules, the drug dose passed through the nasogastric tube (n=3) was 88.1% for spironolactone and 96.4% for warfarin (as sodium salt), calculated of the average drug content in the capsules. The filler in these capsules was lactose (particle-size grade < 355 µm). For size 1 hard gelatine capsules, 90.3% (n=10, $P<0.05$) of the drug dose passed through the tube (drug sotalol hydrochloride, filler MCC).

Blockage of the nasogastric tube during drug administration was occasional, in most cases with no clear correlation to the type of the formulation. However, some tendency towards more frequent blockage was observed with formulation in which there was a combination of the slightly soluble drug dipyridamole and the practically insoluble, but swellable excipients MCC or SMCC.

Discussion

Finnish studies have presented *extemporaneously* compounded oral powders and capsules as a feasible choice for delivering paediatric medications (nifedipine) in hospital environment (10,16,17). The results of the present study demonstrate that, when needed, compounded solid dosage forms can successfully be obtained also for a range of other drug substances which are commonly used in paediatric medication in Finnish hospitals; in most cases, formulations of dipyridamole, spironolactone, warfarin and sotalol were found to be within acceptable limits for content uniformity, as described in the European Pharmacopoeia. In statistical analysis, no significant differences existed in average drug content when sachets were compared to capsules, indicating that both dosage forms are as good as a choice. However, the actual drug content in both dosage form types, sachets and hard gelatine capsules, was generally smaller than the theoretical amount of the drug. In 19 batches out of

24 the difference was statistically significant ($P<0.05$).

The findings on lower drug contents compared to the theoretical drug amount could partly be explained by the fact that the commercial tablets, which were used as a source of the active drug substance, may have contained less drug than labelled. Although the amount of drug was on an acceptable level in all products, the commercial tablets are allowed to have this kind of specific variation in drug content. Additionally, the drug adsorption on the surface of the dispenser or the loss of drug during the preparation process are possible explanations for low drug recovery (10,16). The drug loss has been found to be more marked with small size oral powders (mass 50 mg or 100 mg) dispensed in sachets, in which the drug recovery was only 62-77% of the theoretical value. A total of 75% of the missing drug dose was found on the sachet paper (16). In compounded capsules (capsule shells size 1, 3 or 4) the drug recovery was satisfactory, which apparently related to the smaller surface area of the dispenser; capsule shell compared to sachet paper (10). In our study, the dosage units were in general larger (mass in the sachets varied from 200 mg to 500 mg, and the capsule shell size from 1 to 0) than in the previous study and thus, not so marked drug loss was expected. However, the phenomenon of drug adsorption on the surface of the sachet paper was easily visualised with the yellowish drug dipyridamole. In analysis, at highest 16% of the theoretical dose was found on the sachet paper (formulation containing lactose as filler). The risk of drug loss should be kept in mind in sachet formulations, especially if small sachets are prepared. Also, further studies would be beneficial in evaluations on whether other sachet materials than waxed powder paper could result in smaller drug loss, such as plastic laminates or foil.

Although sachets and hard gelatine capsules were successfully compounded from commercial tablets in most cases, our results emphasize that the type and amount of excipients in the formulation should be considered as they can affect conformity of the dosage form. In statistical analysis, the effect of excipient was found significant in all cases, and formulations which contained the different excipients (MCC, SMCC and lactose, two grades) differed in average drug content. If the quality of

the formulations was evaluated as described in the European Pharmacopoeia, in total of three batches (out of 24 batches) failed to pass the test for content of uniformity; two of these were compounded as sachets (weight 200 mg) and one was a batch of hard gelatine capsules (capsule size 1). The sachets are filled by weight, and therefore inaccuracy of weighing procedures of the small amounts may be a challenge (10). Consistently in our study, the non-conformity in sachets was observed in the smallest sachet mass. Drug adsorption on the surface of the sachet paper or the equipment during preparation seemed possible explanations for non-conformity, as discussed earlier for sachets containing lactose (drug dipyridamole). It has been proposed that use of microcrystalline cellulose as filler could yield in better conformity in sachets (10). The smaller density of MCC results in larger volume of powder, which may protect against the drug adsorption to the sachet paper. Our results emphasise that in addition to density, also other powder characteristics may be important. The best drug recovery and less variation in uniformity of content of dipyridamole was obtained with silicified MCC, in which case not only the small density of the filler but also the surface properties of the excipient, such as hydrophobicity, may explain the results.

Whereas the sachets are filled by weight, capsules are filled with volume. Thus, in preparation of capsules good flow properties of the filler are expected to result in better conformity (10). In general, higher density grades of fillers have improved flow properties (27). In addition, the amount of drug is known as a critical variable in compounded capsule formulations, and small amounts of drug increase the risk for non-conformity (18). In the present study, all 14 batches of capsules which contained lactose as filler complied the test for uniformity of content. On the other hand, in MCC capsules one batch of capsules out of three failed the test. The good conformity of lactose capsules may be explained by the high bulk and tapped densities of lactose, which could result in uniform filling of capsule shells during the manufacturing process. It was noteworthy, that content uniformity (as described in the European Pharmacopoeia) was obtained for a range of drug doses (from 0.1 mg to 2 mg for warfarin and from 0.5 mg to 6 mg for spironolactone), including the small doses of the

drug. In most cases, no statistically significant effects were found in relation to batch to batch variation. This indicates that compounding of such formulations is rather reproducible. However, it should be noted that the measured drug content in the batches was predominantly significantly lower than the theoretical amount of the drug, although the batches met the pharmacopeial requirements. Discrepancy between the results could be explained by the fact that the limits of acceptance are calculated of the average drug content of the batch (instead of labelled drug amount).

The last part of the study evaluated the practical usability of compounded sachets and capsules. Both sachets and capsules, whose contents are emptied for use, seem feasible choice from quality perspective (uniformity of content), and are a practical choice for manufacture in hospital pharmacies. In comparison to sachets, manufacture of capsules is faster as serial production can be utilised. This increases the usability of compounded capsules even further. Capsules filled with the Feton Fastlock filling machine were as good in quality as the reference capsules which had been filled using the automated Quantos capsule filling device. Despite of these favourable properties, there might be some concerns in practical use of compounded sachets and capsules. Including the capsules prepared with the Quantos capsule filling device, the risk of drug loss in manufacture and consequent possibility to under dosing should be considered. In addition, administration of these kinds of solid dosage forms (suspended in fluid) through the nasogastric tube has been found challenging (19,20). The volume of water (or other fluid such as milk) in which the solid powder is suspended, should be rather small as the daily intake of fluids in the neonates is limited. The small volume of fluid increases, however, the risk of blockage of the nasogastric tube. In our study, the administration through a nasogastric tube resulted in loss of drug. The lowest simulated drug doses were obtained with sachets which contained the slightly soluble (but swellable) excipient, microcrystalline cellulose, compared to formulations which contained the more readily soluble lactose. Similarly, the amount passed through the tube was slightly less for the insoluble drug spironolactone **than for** the readily soluble warfarin sodium. Such drug loss in administration,

together with the fact that the actual dose of drug was in most formulations less than the theoretical dose, increases the risk for under dosing in practice, especially for the drugs of narrow therapeutic index (such as warfarin in the present study).

The results emphasize that in compounded sachets and capsules (if the dose is aimed to be administered through a nasogastric tube) solubility of the drug and excipients should be considered. The amount of solid contents should also be as small as possible as the amount of liquid used for suspending cannot be increased due to physiological reasons. This is supported by findings for size 1 capsules, in which the drug administration through nasogastric tube resulted in high simulated drug dose, even though the formulation contained the slightly soluble excipient MCC. Also from the therapeutic point of view, smaller amount of excipients would be preferable as the safety of many excipients in the very young patients is not known (15). In practice, this means preference for compounding sachets of small weight and capsules of small size. The risk of drug loss should, however, be kept in mind.

It is evident that more studies are needed in evaluations on how the formulation and excipients, or their administration procedure to the patient affect bioavailability of *extemporaneous* formulations. Also, *in vitro* studies predicting biological properties of the developed formulations are needed, such as dissolution studies. Unfortunately, the lack of facilities (analytical facilities, dissolution apparatus etc.) in hospital pharmacies has limited conductance of these studies.

Conclusions

Our results indicate that compounded formulations, which meet the quality requirements for uniformity of content as described in the European Pharmacopoeia, can successfully be obtained for a range of drug substances. The results emphasize, however, that the type and amount of excipients in the formulation should be considered. Good conformity of capsules was obtained using lactose monohydrate as filler, whereas microcrystalline cellulose seemed a better choice in sachets. In lactose

capsules content uniformity could be obtained for a range of drug doses, including the very small doses. If the drug is aimed to be administered through a nasogastric tube, solubility of the drug and excipients should be considered, as they were found to affect the simulated drug dose in administration. The risk of drug loss should be considered in manufacture and administration. It is noteworthy that even though the formulations met quality requirements for uniformity of content, in most cases the measured drug content was statistically significantly lower than the theoretical amount of the drug.

Both sachets and capsules could be a practical choice as solid dosage forms to be prepared in hospital pharmacies. Capsules are faster to manufacture, which increases their value even more compared to sachets. It is obvious, however, that validation of manufacturing procedures and quality assurance systems are important in hospital pharmacies, as the conformity is affected by the formulation. In compounding, the risk of drug loss should be kept in mind and analytical methods would be needed to determine the drug amount in quality analysis, or the influence of procedures (crushing the tables) on drug. Additionally, compatibility and stability studies are needed if compounded formulations are manufactured for storage, in addition to *extemporaneous* preparation. Dissolution studies would be needed to predict the biological properties of the developed formulations.

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References

1. Conroy S, Choonara I, Impicciatore P, Mohn A, Arnell H, Rane A, Knoeppel C, Seyberth H, Pandolfini C, Raffaelli MP, Rocchi F, Bonati M, Jong G, de Hoog M, van den Anker J.. Survey of unlicensed and off label drug use in paediatric wards in European countries. European Network for Drug Investigation in Children. *BMJ* 2002; 320: 79–82.

2. Turner S, Longworth A, Nunn AJ, Choonara I. Unlicensed and off label drug use in paediatric wards: prospective study. *BMJ* 1998; 316: 343–345.

3. European Medicines Agency (EMA) 2012: 5-year Report to European Commission, General report on the experience acquired as a result of the application of the Paediatric Regulation. EMA/428172/2012; http://ec.europa.eu/health/files/paediatrics/2012-09_pediatric_report-annex1-2_en.pdf. (accessed 28 March 2016).

4. European Medicines Agency (EMA) 2015. Annual report on benefits and infringements under the Paediatric Regulation. EMA/133100/2015; http://ec.europa.eu/health/human-use/paediatric-medicines/developments/index_en.htm. (accessed 28 March 2016)

5. Brion F, Nunn AJ, Rieutord A. Extemporaneous (magistral) preparation of oral medicines for children in European hospitals. *Acta Paediatr* 2003; 92: 486-490.

6. Standing JF, Tuleu C. Pediatric formulations- Getting to the heart of problem. *Int J Pharm* 2005; 300: 56-66.

7. Teng J, Song CK, Williams RL, Polli JE. Lack of medication dose uniformity in commonly split tablets. *J Am Pharm Assoc* 2002; 42: 195–199.

8. Rosenberg JM, Nathan JP, Plakogiannis F. Weight variability of pharmacist-dispensed split tablets. *J Am Pharm Assoc* 2002; 42: 200–205.

9. Breitkreutz J, Wessel T, Boos J. Dosage forms for peroral drug administration to children. *Paediatr. Perinatal Drug Ther* 1999; 3: 25-33.

10. Helin-Tanninen M, Naaranlahti T, Kontra K, Savolainen K. Nifedipine capsules may provide a viable alternative to oral powders for paediatric patients. *J Clin Pharm Ther* 2007; 32: 49–55.

11. Woods DJ 1997. Extemporaneous formulations: problems and solutions. *Pediatr Perinat. Drug Ther* 1997; 1: 25-29.

12. Barnes AR, Nash S. Stability of bendroflumethiazide in a low-dose extemporaneously prepared capsule. *J Clin Pharm Ther* 1994; 19: 89-93.

13. Fortner J, Salton J, Carlson C, Wheeler R, Cote B, Rao D. Solid state stability of extemporaneously prepared levothyroxine aliquots and capsules. *Int J Pharm Compd* 2015; 19(5): 414-419.

14. Stoltenberg I, Breitkreutz J. Orally disintegrating mini-tablets (ODMTs) – A novel solid oral dosage form for paediatric use. *Eur J Pharm Biopharm* 2011; 78: 426-469.

15. Ernest TB, Elder DP, Martini LG, Roberts M. Developing paediatric medicines: identifying the needs and recognizing the challenges. *J Pharm Pharmacol* 2007; 59: 1043-1055.

16. Helin M, Kontra K, Naaranlahti T, Wallenius K. Content uniformity and stability of nifedipine in extemporaneously compounded oral powders. *Am J Health-Syst Pharm* 1998; 55: 1299–1301.

17. Helin-Tanninen M, Naaranlahti T, Kontra K, Wallenius K. Enteral suspension of nifedipine for neonates. Part 1. Formulation of nifedipine suspension for hospital use. *J Clin Pharm Ther* 2001; 26: 49–57.

18. Mathaut S, Bordenave J, Fratta A, Benoit G. Quality control of hospital preparations: results concerning capsules production in a child hospital. *Annal Pharmaceutiq Franc* 2006; 64: 44–51.

19. Williams NT. Medication administration through enteral feeding tubes. *Am J Health-Syst Pharm* 2008; 65: 2347-2357.

20. Belknap DC, Seifert CF, Petermann M: Administration of medications through enteral feeding catheters. *Am J Crit Care* 1997; 6 (5): 382–92.

21. World Health Organization (WHO) 2010. WHO Model List of Essential Medicines for Children http://www.who.int/medicines/publications/essentialmedicines/Updated_second_children_list_en.pdf (accessed 28 March 2016)

22. Rowe RC et al. eds. Handbook of Pharmaceutical Excipients.Eds., 7th edn. Pharmaceutical Press, 2012

23. Allen LV Jr, Erickson M A: Stability of baclofen, captopril, diltiazem hydrochloride, dipyridamole, and flecainide acetate in extemporaenously compounded oral liquids. *Am Society of Health Syst Pharm* 1996; 53: 2179-2184.

24. Alexander KS, Vangala SS, Dollimore D. An improved high-performance liquid chromatography assay for spironolactone analysis. *Drug Dev Ind Pharm.* 1998; 24(2):101-107.

25. Ghimenti S, Lomonaco T, Onor M, Murgia L, Paolicchi A, Fuoco R, Ruocco L, Pellegrini G, Trivella MG, Di Francesco F. Measurement of Warfarin in the Oral Fluid of Patients Undergoing Anticoagulant Oral Therapy. *PLoS One* 2011; 6(12):e28182. doi: 10.1371/journal.pone.0028182.

26. Santoro MIRM, Tsubone C, Gomes FP, Kedor-Hackmann ERM, García PL. Development and validation of high performance liquid chromatographic and UV – derivative spectrophotometric methods for the determination of sotalol hydrochloride in tablets. *Anal Letters* 2008; 41(11): 2044-2057.

27. Lahdenpää E, Niskanen M, Yliruusi J. Study of some essential physical characteristics of three Avicel PH grades using a mixture design. *Eur J Pharm Biopharm* 1996; 42: 177–182.

TABLES

Table 1. Uniformity of content in compounded sachets. Individual contents of at least 10 units were determined, as described in the method by European Pharmacopoeia.

Drug; Excipient	Average drug content (mg)	Acceptable ± 15% limits (mg)	Largest individual deviation (mg)	Maximum deviation (%)	Amount of drug (% of theoretical)
Dipyridamole[a]					
MCC	4.52[f,g]	3.84 – 5.20	1.18	+26.3	90.4
SMCC	5.33[f,g]	4.54 – 6.13	0.69	–12.9[e]	106.6
Lactose (< 355 µm)	4.04[f,g]	3.43 – 4.65	0.52	+12.9[e]	80.8
Lactose (< 250 µm)	4.46[f,g]	3.79 – 5.13	1.37	–30.7	89.2
Spironolactone[b]					
Lactose (< 355 µm)	0.44[f]	0.37 – 0.51	0.04	+9.0[e]	88.0
Warfarin (as sodium salt)[c]					
Lactose (< 355 µm)	0.092	0.078 – 0.106	0.009	+10.2[e]	92.0
Sotalol (as hydrochloride salt)[d]	3.69	3.14 – 4.23	0.17	–4.6[e]	92.2
MCC					

Theoretical drug content (powder mass) [a]5 mg (200 mg); [b]0.5 mg (500 mg); [c]0.1 mg (500 mg); [d]4 mg (300 mg); [e]Complies with the test for Uniformity of Content (European Pharmacopoeia); [f]Statistically significantly different ($P<0.05$) from the labelled amount of drug; [g]Statistically significantly different ($P<0.05$) when one excipient (MCC, SMCC or lactose) is compared to the other excipient.

Table 2. Uniformity of content in compounded hard gelatin capsules. Individual contents of at least 10 units were determined, as described in the method by European Pharmacopoeia.

Drug; Theoretical drug content	Average drug content (mg)	Acceptable ± 15% limits (mg)	Largest individual deviation (mg)	Maximum deviation (%)	Amount of drug (% of theoretical)	Average capsule content (mg)
Spironolactone[a]						
0.5 mg	0.424[d]	0.360 – 0.487	0.089	+21.0[c]	84.4	552.4
0.5 mg	0.402[d]	0.342 – 0.462	0.006	–1.7[c]	80.4	556.3
0.5 mg	0.426[d]	0.362 – 0.489	0.017	–4.0[c]	85.2	553.3
3 mg	2.58[d]	2.19 – 2.97	0.24	–9.4[c]	86.0	545.6
6 mg	5.25[d,e]	4.47 – 6.04	0.43	+8.1[c]	87.5	536.1
6 mg	4.88[d]	4.15 – 5.61	0.25	–5.2[c]	81.3	545.8
6 mg	5.02[d]	4.27 – 5.77	0.18	–3.5[c]	83.7	544.4
Warfarin (as sodium salt)[a]						
0.1 mg	0.082[d,e]	0.070 – 0.095	0.006	–7.0[c]	82.0	530.1
0.1 mg	0.094	0.080 – 0.108	0.001	–1.2[c]	94.0	522.1
0.1 mg	0.090	0.076 – 0.103	0.007	–8.2[c]	90.0	486.5
0.2 mg	0.187[d]	0.160 – 0.216	0.010	–5.5[c]	93.5	512.1
2 mg	1.89[d]	1.60 – 2.17	0.07	+3.5[c]	94.5	509.2
2 mg	1.84[d]	1.56 – 2.11	0.12	–6.5[c]	92.0	521.0
2 mg	1.86[d]	1.58 – 2.14	0.07	+3.7[c]	93.0	521.7
Sotalol (as hydrochloride salt)[b]						
4 mg	3.72[d]	3.16 – 4.28	0.13	–3.5[c]	93.0	186.8
4 mg	3.70	3.14 – 4.25	0.93	–25.2	92.5	180.6
4 mg	3.70[d]	3.15 – 4.26	0.38	–10.4[c]	92.5	173.0

[a] Capsule size 0, filler lactose monohydrate, particle-size < 355µm; [b] Capsule size 1, filler MCC, particle size < 100µm, [c]Complies with the test for Uniformity of Content (European Pharmacopoeia)
[d]Statistically significantly different ($P<0.05$) from the labelled amount of drug; [e]Statistically significantly different ($P<0.05$) when the batch is compared to parallel batches. When capsules were compared to sachets containing the same drug substance, at the same dose (Table 1.), no statistically significant effects were detected (N.S.).

Figure legends

Figure 1. Visualisation of the adsorption of the yellowish drug dipyridamole on the sachet paper. Formulations (powder mass 200 mg) were dispensed in sachets, similarly as in preparation of the compounded solid dosage forms, and emptied for analysis. Formulations contained the different excipients (order of emptied sachet papers from front to back); SMCC, lactose monohydrate (particle size < 250 µm), MCC and lactose monohydrate (particle size < 355 µm).

Figure 2. Drug content of capsules prepared using the automated Quantos (Mettler Toledo) capsule filling device; upper panel spironolactone (theoretical drug amount 0.5 mg, n = 30), lower panel warfarin (theoretical drug amount 0.1 mg, n = 20). The batches complied with the content uniformity test, as specified in the European pharmacopoeia. The acceptance ± 15% limits were 0.340 mg – 0.472 mg and 0.079 mg – 0.107 mg for spironolactone and warfarin, respectively. For spironolactone, the drug amount was found significantly different ($P<0.05$) from the labelled amount. No statistical effects were found for warfarin (N.S.).